Applicants respectfully request re-evaluation of the response submitted September 29, 1999 and reconsideration of the pending rejections, in light of the following remarks.

REMARKS

Claims 1-14 are pending for prosecution in the present application. The claims as pending are provided in an attached appendix for the Examiner's convenience. Applicants believe that the amendments, submitted September 29, 1999 were entered upon filing of the Notice of Appeal. In any event, the Advisory Action states that the arguments have been considered. Thus, Applicants' response is to the comments made in the Advisory Action.

The Advisory Action mailed October 15, 1999 states that Applicants' last response (submitted September 29, 1999) "merely reiterates arguments previously presented and answered." Applicants respectfully point out that the response cited above identifies that Pötgens et al. (J. Biol. Chem 269: 32879-85 (1994)) specifically addressed whether their mutants inhibited the activity of wild-type VEGF. To quote, "In no case did any mutant inhibit the activity of the wild type protein. On the contrary, at the highest concentrations of some mutants the biological response was slightly enhanced." (Page 32883, left column).

The above quotation has apparently not previously been considered by the Examiner. The Office Actions have not addressed this issue during the prosecution of this application. This statement precludes the VEGF mutants disclosed in Pötgens et al. from anticipating the presently claimed invention.

The Pötgens et al. reference is the principal basis for the 35 U.S.C. § 102 and 103 rejections of the present case. Not only does the statement quoted above show that the VEGF mutants of Pötgens et al. do not anticipate the present invention, but it also casts doubt on the inherency of the VEGF mutants disclosed by Claffey et al. (Biochim. Biophys. Acta 1246: 1-9 (1995)) to have all the features of the present invention. The requirement of reasonable certainty that a disclosed product actually possess the features of a claimed invention for an inherency argument to apply removes this reference as an anticipatory bar to the present application. With the elimination of these two references as anticipatory to the present claims, there remain no bars to the present application passing to issue.

The Examiner is directed to the response submitted September 29, 1999 for a more detailed discussion of the above issues. Specifically, the Examiner is requested to acknowledge that Pötgens et al. states, "In no case did any mutant inhibit the activity of the wild type protein." To anticipate a claim, each and every element must be disclosed. Pötgens et al. does not disclose antagonists, as claimed. In fact, Pötgens et al. teaches away from the claimed invention. Moreover, Pötgens et al. supports that mutants can enhance activity, rather than antagonize activity.

On the basis of the remarks presented herein, in combination with the amendment and the remarks presented in the response of September 29, 1999, we believe that this application is now in condition for immediate allowance and respectfully request the Examiner to withdraw the outstanding rejections and pass this application to issue.

Respectfully submitted,

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APPENDIX

1. (Twice Amended) A vascular endothelial cell growth factor (VEGF) antagonist molecule comprising a variant VEGF polypeptide, said variant polypeptide comprising an amino acid modification of at least one cysteine residue, wherein said amino acid modification inhibits the ability of said variant polypeptide to properly dimerize with another VEGF polypeptide monomer, wherein said antagonist molecule is capable of binding to VEGF receptors without significantly inducing a VEGF response, wherein said antagonist molecule is capable of inhibiting a biological activity of a native VEGF protein.

2. The antagonist molecule according to Claim 1 wherein said amino acid modification is a substitution of said at least one cysteine residue with a different amino acid which is incapable of participating in a disulfide bond.

3. The antagonist molecule according to Claim 2 wherein said substitution is of the cysteine residue at amino acid position 51 and/or 60 of the native VEGF amino acid sequence.

4. The antagonist molecule according to Claim 3 wherein aspartic acid is substituted for cysteine.

5. The antagonist molecule according to Claim 4 comprising the substitution C51D.

6. The antagonist molecule according to Claim 4 comprising the substitution C60D.

7. The antagonist molecule according to Claim 1 wherein said amino acid modification is a chemical modification of said at least one cysteine residue which renders said cysteine residue incapable of participating in a disulfide bond.

8. The antagonist molecule according to Claim 7 wherein said chemical modification is of the cysteine residue at amino acid position 51 and/or 60 of the native VEGF amino acid sequence.

9. The antagonist molecule according to Claim 1 containing further amino acid modifications that do not otherwise affect the essential biological characteristics.

10. An isolated nucleic acid sequence comprising a sequence that encodes the VEGF antagonist molecule of Claim 1.

11. A replicable expression vector capable in a transformant host cell of expressing the nucleic acid of Claim 10.

12. Host cells transformed with the vector according to Claim 11.

13. Host cells according to Claim 12 which are Chinese hamster ovary cells.

14. A composition of matter comprising the VEGF antagonist molecule according to Claim 1 compounded with a pharmaceutically acceptable carrier.